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Co-Crystal: An Overview on the Novel Techniques for the Formation of Co-Crystal and Its Potential Benefit in the Pharmaceutical Industry

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ABSTRACT

A pharmaceutical co-crystal is a multi-component system in which at least one component is an Active Pharmaceutical Ingredient and the other component is a pharmaceutically acceptable component. Co-crystallization of drugs with co-formers, for example, is a promising new approach to improving drug performance, solubility, dissolution profile, pharmacokinetics, and stability. This review provides a comprehensive overview of pharmaceutical co-crystals, including preparation methods, physicochemical properties, and uses. In addition, some examples of drug co-crystals are highlighted to explain the effect of crystal structure on various aspects of the active ingredient of the drug, such as physical stability, chemical stability, mechanical properties, optical properties, bioavailability, sustained release, and therapeutic effect. This review provides more efficient design and application guidance.

INTRODUCTION

Physicochemical properties such as drug Active pharmaceutical ingredient (API) stability, particle size, powder fluidity, taste, hygroscopicity, solubility, and tolerability are important factors that affect the therapeutic effect and manufacturing cost of solid formulations [1]. In oral drug delivery systems, gastrointestinal absorption is highly dependent on the solubility and rate of dissolution of drug molecules. However, currently, about 90% of new chemicals and 40% of the drugs currently on the market belong to the "BCS" biopharmaceutics classification system, Class II and IV[2] suffering from the problems of water solubility and low bioavailability. Due to this, the absorption of the drug in the gastrointestinal tract is restricted, and as a result, the clinical use of the drug is hindered. Obviously, the physicochemical properties of pharmaceutical solids have a significant impact on drug performance. It is well known that atomic packing in unit cells and crystal lattices directly affects the properties of a particular crystalline material. Therefore, changes in the physicochemical properties of solid dosage forms can be achieved by adjusting the crystal packing arrangement [3,4]. So far, multiple solid-state strategies have been applied to tune API properties such as salt [5], polymorphs [6], hydrates [7], solves[8], co-crystals[9,10] (Figure 1). However, these approaches have limitations. For example, hydrates/solvates are often unstable because only molecules with suitable ionizable groups are suitable for salt formation and water / solvent molecules tend to be lost over time. I have. By comparison, any drug (whether acidic, basic, or non-ionized form) can form a co-crystal with the appropriate coformer[3]. Over the last two decades, pharmaceutical co-crystals have received a great deal of attention from academia and the pharmaceutical industry as they have the potential to improve the physicochemical properties of APIs by changing their crystal structure without changing their pharmacological properties [11,12]. With the development of the co-crystal field, several pharmaceutical co-crystals such as Steglatro and Entresto have been approved and are in clinical trials [13-16]. Pharmaceutical co-crystals contained two or more individual neutral molecules in chemical ratio and were bound via non-covalent interactions (hydrogen bonds, van der Waals, stacking interactions, etc.) are defined as crystals. The components are APIs and the others are pharmaceutically acceptable ingredients [17]. Since the early 2000s, co-crystal engineering has had the potential to be a potential approach to improving the physicochemical properties of pharmaceuticals, in some of the leading pharmaceutical co-crystal publications 2003-2004,[18-20] It is recognized that it is contributing. This pioneering work emphasized the role of crystal engineering and supramolecular synthons in drug-based

co-crystal design and supported the development of co-crystal approaches to improve drug performance. Numerous robust supramolecular synthons have been identified and have been shown to play an important role in the design of co-crystals. Some common functional groups are particularly suitable for the formation of supramolecular synthons from co-crystals such as carboxylic acids, amides, and alcohols [21,22]. There are two different categories of supramolecular synthons, including supramolecular homosynthons and supramolecular heterosynthons18. Supramolecular Hoisington is formed by self-complementary functional groups such as carboxylic acid dimers and amide dimers [23]. Conversely, supramolecular heterosynthons are organized by distinct but complementary functional groups (e.g., carboxylic acid-pyridine18 and alcohol-aromatic nitrogen [24] hydrogen bonds). With the rapid development and increasing applications of pharmaceutical co-crystals, the importance of pharmaceutical co-crystals has become a regulatory concern. In 2011, the U.S. Food and Drug Administration (FDA) classified drug co-crystals as drug intermediates and classified them as "separable API-excipient molecules in which both API and excipients are in the same crystal lattice." We first published draft guidance that defines it as a "complex" [14,25]. However, industry and academic researchers believed that this definition was too simple to make a clear distinction between co-crystals. In 2016, the FDA's revised guidelines describe co-crystals as "crystal materials composed of two or more different molecules in the same crystal lattice linked by non-ionic and non-covalent bonds." [26]. In 2018, the FDA stated that co-crystals of pharmaceuticals are "composed of two or more different molecules, one of which is the API, with non-ionic and non-covalent bonds at defined chemical ratios within the same crystal lattice. Crystalline material bonded in. " A conformer is a "component that interacts non-ionic with APIs in the crystal lattice, is non-solvent (including water), and is usually non-volatile" [27]. The European Pharmaceutical Agency (EMA) states that co-crystals are "homogeneous (single-phase) crystal structures consisting of two or more components of a particular chemical ratio, and the crystal lattice arrangement is not based on ionic bonds (salts). As in the case of[28]. Compared to the FDA's definition of co-crystal, the EMA described co-crystal as a viable alternative to the salt of the same active ingredient [28]. In other words, co-crystals are equivalent to APIs, except that they have different pharmacokinetic properties [29]. This review summarizes recent advances in pharmaceutical co-crystals, including methods of preparing and modulating physicochemical properties and applications of co-crystals. Solution-based processes (including solvent evaporation, antisolvent processes, cold crystallization, reaction co-crystallization, and slurry conversion) and solid-based processes (clean milling, liquid-assisted milling, and melt crystallization) are

presented. The following describes various modulation characteristics and applications of co-crystals, including physical and chemical stability, mechanical and optical properties, in vitro and in vivo performance.

CO-CRYSTALS:-

Crystallization is defined as changing physical properties by modifying a drug at the molecular level. The co-crystallization process requires the drug and the co-crystal to form a co-crystal. co-crystals are two or more chemicals in which all components are in a chemical ratio and contain drug modifications to change the physical properties of the drug, in particular, the solubility of the drug, without altering its pharmacological activity. It is a multi-component molecular crystal composed of different molecules.

APPLICATION OF CO-CRYSTAL IN FORMULATION DEVELOPMENT

co-crystal is defined as changing the physicochemical properties of a drug at the molecular level. That is, there are no other additives, as the physicochemical properties of the drug can be adjusted and various methods applied to improve it. Improvement of physicochemical properties of substances [30]. The properties of active substances and conformers, the properties of molecular interactions between them, and the method of synthesis are important, changing only the physicochemical properties and not the pharmacological properties. Element. The impact on the physicochemical properties of the API depends on the available coformers [31,32]. Pharmaceutical co-crystals can improve drug physicochemical properties such as melting point, tablet ability, solubility, stability, bioavailability, permeability, and these properties are highlighted here as inappropriate examples. increase.

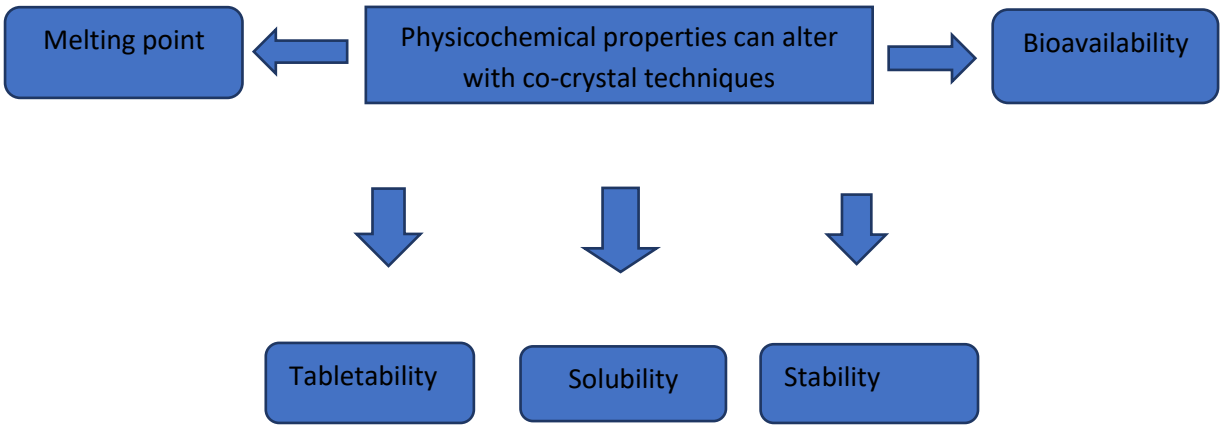


Fig.No.1 Application of Co Crystal in formulation development [31-36]

Melting point: -

It is one of the physical properties of a solid and is used to determine its purity. Pure substances or solids melt at a sharp, narrow melting point. The thermodynamic stability of each API can be determined by its melting point. Therefore, there is a usefulness of the melting point conformer, which is also useful for highly stable and heat-labile drugs. Therefore, for co-crystals, the choice of conformer is very important. Synthetic. Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are the most commonly used techniques for determining melting points. Zhang. We studied the synthesis of carbamazepine co-crystals using nicotine amide and saccharin as conformers in two different solvents, such as an ethanol-water mixed solvent and a polyvinylpyrrolidone (PVP) solution. The authors use differential scanning calorimetry to determine the melting point of the co-crystals, and for the DSC curve of the starting material, carbamazepine and nicotinamide in the ethanol-water mixture, melting near 195°C and 132°C. I observed. C, respectively. The formed co-crystals then showed a single heat absorption peak at about 162°C between the melting points of carbamazepine and nicotine amide, whereas carbamazepine and saccharin in the ethanol-water mixture were around 176 ° C and 181°C. Showed melting at, and the formed co-crystals showed melting. The 173 ° point pointed to C17. Jadhav *et al*. (Melting point studies of fenofibrate co-crystals formed with different conformers such as Para-aminobenzoic acid, benzoic acid, salicylic acid has also been studied, the melting point of pure fenofibrate is 7882°C, and conforms such as Para-aminobenzoic acid. Acid, benzoic acid, and salicylic acid, which were observed to be the melting points of mer, were 184186°C, 158160°C, and 122124°C, respectively, but the melting points of the formed conformers were 7678°C and 7476°C, respectively., 7072°C. The melting point of fenofibrate was lower than the melting point of a pure single conformer. Co-crystals were synthesized and the difference in melting point between the drug and the co-crystal was studied. The melting points of sodium acetate and saccharin-sodium coformer were previously high but decreased after the formation of co-crystals with piroxicam, and the melting points of the co-crystals of urea, nicotine amide, and resorcinol increased [33].

Tabletability:-

Tabletability means the ability of a substance to form a tablet. Crystal packing, tableting, and compression are important parameters of prescription research. With the help of co-crystallization, these properties can be modified using the appropriate conformers. Zheng-

zheng *et al*. synthesized co-crystals of resveratrol and the conformers 4-aminobenzamide and isoniazid and studied their improved solubility and tablet ability. The authors found that tablets made of resveratrol 4-aminobenzamide co-crystals have tensile strengths in excess of 3 MPa at a compressive pressure of 250 MPa, even with high pressure and laminated tablets of 0.6 MPa due to the low tableting properties of RES. I found that. The authors concluded that co-crystal formation improved the tablet ability of the drug. The densification behavior of the co-crystals of paracetamol with trimethylglycine and oxalic acid was found to be superior to that of the drug alone. The tablet ability of resveratrol was improved by the formation of co-crystals with 4-aminobenzamide and isoniazid. co-crystals showed higher tableting properties than neat drugs or coformers. The mechanical properties of the API can be adjusted by changing the crystal packing by co-crystallization, and the co-crystals of the vanillin isomers with the same coformer showed higher tableting properties than the isomers and co-formers. Paracetamol has low compressibility, and to overcome this problem, paracetamol tablets are usually manufactured using a wet granulation process. This is a very tedious task to solve this problem, Latif *et al.*A paracetamol co-crystal was synthesized to improve the compression or tableting properties of paracetamol. The author used caffeine as a conformer to prepare paracetamol co-crystals, such as by dry milling. We observed an increase in liquid-assisted grinding, solvent evaporation, poor solvent addition, and paracetamol compressive and mechanical properties.

Solubility: -

As mentioned in the introduction, about 60-70% of drugs belong to BCS II (low solubility/high osmolarity) and IV (low solubility/low osmolarity) classes 1, so improvement is needed. improve the solubility of these drugs for development. different formulas. With the development of co-crystals, it is possible to increase the solubility of drugs, many researchers have improved the solubility of drugs by this technique. E.g., Mounika *et al.*developed Fexofenadine crystals using tartaric acid as a fixative by solvent evaporation technique and studied the crystals for saturation solubility according to the method of Higuchi and Connors. The author carried out a study on the solubility of the drug with water as well as 0.01 N HCl and found that the solubility of the crystals in water was 11 times higher than that of the pure drug, and the solubility of the crystals was 11 times higher. body in 0.01 N HCL is 2.47 times greater. of pure medicine [22]. Iyan *et al*. developed the co-crystallization of nicotinamide simvastatin by solvent evaporation to improve the solubility of simvastatin by co-crystallization using nicotinamide as a co-crystallizing agent or copolymer and evaluated on

solubility. It was observed that the saturation solubility of crystals was increased threefold compared with crude simvastatin [23]. Chadha *et al*also improved the solubility of efavirenz by the co-crystallization technique. The author synthesized efavirenz crystals using oxalic acid dihydrate and citric acid monohydrate as a coupling agent to improve the physicochemical properties of solubility and dissolution rate. As both conjugates have high water solubility, 14.3g/100ml and 64.7g/100ml respectively, and contain groups of hydrogen bond donors and acceptors, can be used to design crystals may efavirenz lead to improved solubility [24]. Shubhangi *et al*. synthesized crystals of the sparingly water-soluble drug Darunavir. It is a class II BCS drug with low solubility. co-crystals were grown by cold crystallization using succinic acid as the template. The author determined the water solubility of darunavir by saturation solubility by dissolving an excessive number of crystals in water for 24 h on a rotary shaker, spectrophotometer analysis and observing that with crystallization technique, it has a significant improvement in water solubility, finding the saturation solubility increased by 1.92 times [25]. Author Rajurkar also developed Ezogabine Co crystals to improve water solubility using carboxylic acids as a blender; the technique of co-crystallization and solvent evaporation with the help of ultrasound and found that the solubility of copper crystals was improved by 1011 times compared with pure drug[26]. Muddukrishna *et al*studied the synthesis of paclitaxel and naringenin co-crystal to improve solubility by solvent-assisted milling. Paclitaxel (PTX) is a Class 4 drug; This drug has low water solubility. The solubility study of paclitaxel and naringenin co-crystal was performed at room temperature for 72 h by the shaker method, analyzed the samples by the HPLC method, and found a 2.4-fold increase in solubility at saturation [27]. Prabhakar *et al*also prepared co-crystal from Piroxicam and studied the solubility. The author used different components such as adipic acid, benzoic acid, cinnamic acid, citric acid, glutaric acid, p-hydroxybenzoic acid, hippuric acid, malonic acid, resorcinol, sodium saccharin, 1-hydroxy-2-anaphoric acid, sodium acetate, urea, catechol, ferulic acid, aerosil200, nicotinamide, para-aminobenzoic acid, anthranilic acid, and succinic acid to synthesize co-crystal and achieve saturated water solubility of co-crystal and notice a significant increase solubility of the drug after preparation in the form of crystals [28]. Muddukrishna co-crystalsof Etravirine to improve solubility using tartaric acid as a template with slow evaporation technique. Etravirine is a class IV BCS drug with low solubility and low permeability. The co-crystal solubility study was performed using the shake flask method and showed a 3.6-fold increase in the solubility of co-crystal compared to the pure drug [29].

Stability: -

Research is also required when developing a new formulation. Various studied stability such as chemical stability, thermal stability, solution stability, and optical stability have to be realized during the development of pharmaceutical co-crystals. Iyan 23 et al developed co-crystallization of simvastatin nicotinamide by solvent evaporation to improve the solubility of simvastatin by co-crystallization using nicotinamide as a co-crystallizer or co-former and evaluated for stability study at 40^{o}C and Relative Humidity (RH) 75% for one month found it stable.

Bioavailability: -

Bioavailability is defined as the rate and extent to which a pure drug reaches systemic circulation. The low oral bioavailability of the API is one of the major challenges in developing formulations where, with the help of co-crystallization, one can increase or improve the bioavailability of a drug. Many researchers have improved the bioavailability of various drugs by converting them to co-crystals. E.g., Mounika *et al*prepared crystals of Fexofenadine. Fexofenadine is a BCS class II drug with low solubility and high osmolarity, rate-limiting steps to achieve desired bioavailability. Therefore, the author prepared co-crystallization of fexofenadine using tartaric acid as a co-former by evaporating the solvent and observed that with the co-crystallization technique, maximum drug release was achieved. compared with preparations[22]. Pinky *et al*formulated crystalline tablets in the dosage form of clarithromycin to improve bioavailability. Since clarithromycin is a class II BCS drug, the author prepared crystals using urea as a template by solvent evaporation. Tablet formulations are developed and evaluated. The authors concluded that tablets formulated with clarithromycin co-crystals showed improved in vitro drug solubility and release compared with commercially available tablets. And thus increase the oral bioavailability and therapeutic effect [35]. Zhang *et al* studied the synthesis of Carbamazepine co-crystal using nicotinamide and saccharin as a template by solvent evaporation technique[36].

DIFFERENT STRATEGIES OF CO-CRYSTALS FORMATION: -

To date, researchers have reported completely different strategies for preparing crystals. Several strategies that have previously supported the reaction and milling process have been reported for co-crystal synthesis. Co crystals can be prepared by both solvent and solid methods [37]. Different types of strategies, such as solvent evaporation, crystallization

techniques, the addition of anti-solvent, transfer methods Sludge exchange, and reaction crystallization were used (Figure 1). Recently, several new strategies have been used to form crystals, such as the ultrasonic-assisted method per unit area, the spray drying technique of the important liquid atomization technique, and the hot-softening extrusion, which has begun to appear. According to the methods reported for co-crystal formation, there is still a lot of inconsistency in the application of different methods, The terminology used to describe the details such as solvent selection, the concentration of target molecule/isomer, equilibration time and recovery process are also inconsistent. This inconsistency and miss information make it difficult to repeat or compare methods of co-crystal preparation and will inevitably lead to confusion for those new to this research field. Therefore, the objective of this review is to systematically describe all the reported crystal preparation pathways and applications in one place, with the goal of standardizing the progress made to date in the field.

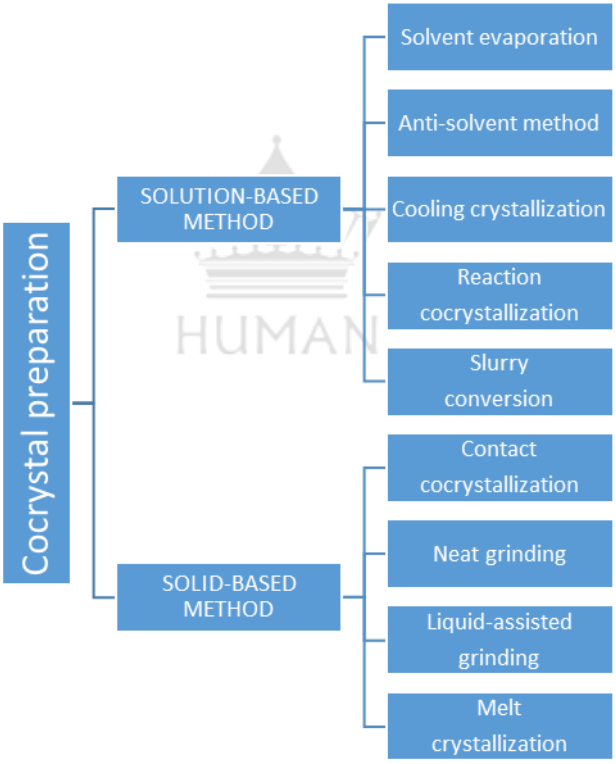


Fig.No.2 Novel method for co-crystal preparation[41-44]

Solution-based methods: -

In these methods, there are tertiary phases (API, coformer, and solvent) in solution, and the perfect state is that the co-crystal is supersaturated while the reactants (API and coformer) are saturated or unsaturated. under experimental conditions. Therefore, the degree of

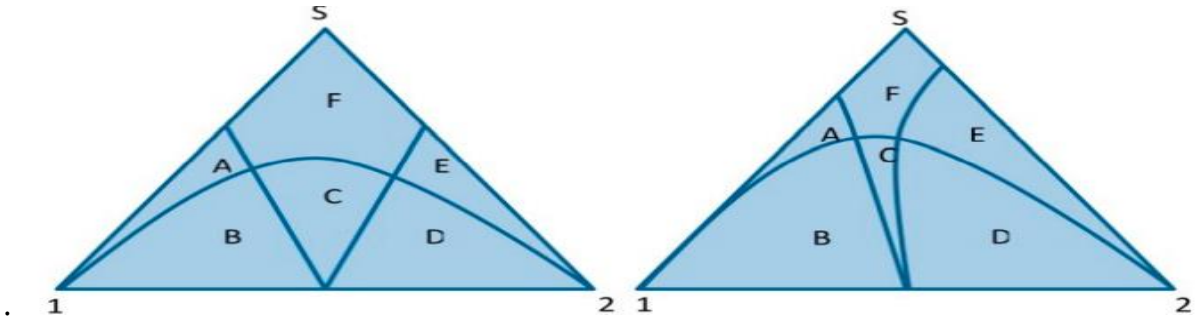
supersaturation for crystals in solution is an important parameter of co-crystallization and can be adjusted by API and coformer [38] concentrations. To guide the crystal formation path, it is necessary to establish a phase diagram that describes the thermodynamically stable conditions, which can ensure that the crystal remains in the thermodynamically stable region and exclude the crystallization of pure reactants. The positions of the thermodynamically stable co-crystal phase regions are mainly determined by the solubility of the reactants [39]. Numbers. Figure 3 shows a tertiary phase diagram, illustrating how supersaturation of a crystal is achieved when the reactants are either saturated or unsaturated, depending on the solubility of the reactants [40]. As shown in Figure 3a, reactants A and B have similar solubility and can saturate simultaneously in the given solvent; therefore, co-crystals can be formed at equivalent reagent concentrations. In Figure 3b, the reactants show different solubilities in solvents of non-congruent saturation, where co-crystal can be produced using non-equivalent concentrations of reactants to achieve is the stable region of co-crystal.

Solvent evaporation method

Solvent evaporation is the most common method for preparing co-crystals and is typically used to synthesize high-quality single-crystal co-crystals suitable for structural analysis by single-crystal X-ray diffraction. In this approach, the co-crystal component is completely dissolved in the appropriate solvent at the appropriate stoichiometric ratio and then the solvent is evaporated to obtain the co-crystal [41]. Solvent choices affect co-crystallization and can affect the solubility of the reactants. In a given solvent, the co-crystalline components must be consistently dissolved. When a co-crystallization process occurs between two disagreeable components, the less soluble component preferentially precipitates, resulting in a dense mixture of co-crystal components and co-crystal components or failure to form a co-crystal. This technique has been used to effectively synthesize many co-crystals [41-43]. For example, acetonitrile, which slowly evaporates at room temperature for 3-5 days, formed a block-like single crystal of 1: 1 febuxostat-piroxicam co-crystals that interacted via carboxylic acid-azezol Clinton. The resulting co-crystals showed higher solubility and better tableting properties than the corresponding components [44]. The co-crystals of nebivolol nicotinamide hydrochloride with improved dissolution rate were recovered by solvent evaporation [45].

Antisolvent method

Antisolvent crystallization has been considered an effective approach to control the quality, particle size, and properties of co-crystals, in which crystallization is conducted in semi-batch or continuous manufacturing processes[46-50] For instance, Chun *et al.*[50] prepared the indomethacin saccharin co-crystals via the antisolvent technique. As shown in Fig., a solution of 0.034 mol/L indomethacin and 0.05 mol/L saccharin was mixed in 150 mL methanol, and 75 mL water (antisolvent) was then added to the solution vessel using a peristaltic pump with a 300-rpm stirring speed at 25C for 1 h. Rod-like or columnar co-crystals with better dissolution rates were achieved. During the crystallization process, the co-crystal solubility is diminished by the addition of antisolvent to reach supersaturation, resulting in the precipitation of co-crystals. Therefore, it is critical to choose the proper miscible solvent combination in which the co-crystal has low solubility in the poor solvent. The ratio of the cosolvent can significantly influence the yield of co-crystals as the composition of the solvent could impact the solubility of the co-crystal and individual components. The yield of carbamazepine–saccharin (CBZ–SAC) co-crystals reached the maximum value when the volume ratio of methanol to water was 1:2; whereas CBZ hydrates would form below that ratio39. In addition, the coformer/drug ratio was also found to be a critical attribute to co-crystal purity and solid yield. In a solution containing less SAC, CBZ hydrates tended to form as impurities during the antisolvent co-crystallization of CBZ–SAC. Since SAC exhibited a higher affinity for water than CBZ, the low content of SAC in the solution would bring more water molecules to coordinate with CBZ for forming CBZ hydrates[47].



3 (a)Similar solubility 3 (b) solubility differences

Figure Schematic representation of isothermal ternary phase diagram. (a) Similar solubilities between the Active Pharmaceutical Ingredient (API) and coformer (1 and 2) insolvent S and (b) different solubilities of 1 and 2 in S. Region A, component 1 and solvent; B, component 1

+ co-crystal; C, co-crystal; D, component 2 + co-crystal; E, component 2 and solvent; F, solution. (Modified from. Copyright 2013 Cell Press).

Cooling Crystallization

It is a less frequently applied method for co-crystal formation. It is a generally slow and time-consuming process as compared to other techniques, for example, darunavir succinic acid co-crystal. In this, there is an improvement in solubility, dissolution, and micrometric properties than its individual drug darunavir. A designed seeded cooling crystallization was used to prepare co-crystals of carbamazepine: nicotinamide from ethanol in an effort to establish a scalable co-crystallization solution strategy. Solvent selection, identification of the thermodynamically stable co-crystal operating range, and de supersaturation kinetics were considered during the design of the process [51].

Reaction co-crystallization

Reaction co-crystallization is suitable for co-crystal formation when the solubilities of the co-crystal components are different. Mixing reactants of non-stoichiometric concentrations to produce a supersaturated co-crystal solution, resulting in a co-crystal precipitate. In this process, co-crystal nucleation and growth are controlled by the ability of the reactants to reduce the solubility of the co-crystal [52]. The formation of meloxicam salicylate co-crystal [53], carbamazepine saccharin co-crystal [54], and indomethacin saccharin co-crystal [55] was achieved by reactive crystallization methods.

Slurry Crystallization

Slurry crystallization is the process of creating a suspension by adding various solvents into a mixture of API and a suitable coformer. The solvent is decanted, then the solid material is dried under a stream of nitrogen for 5 minutes and characterized using PXRD. This method is used to prepare co-crystals after the drug and coformer have stabilized in the solvent [56].

Solid-based methods: -

Solid crystallization is an effective and environmentally friendly method for co-crystal formation as it requires little or no solvent. co-crystals are spontaneously formed by direct contact or grinding at higher energy inputs. These are reasonable alternatives to solution-based co-crystallization methods that can be environmentally dangerous due to their high

solvent consumption. Numerous pharmaceutical co-crystals are synthesized by the solid method [57-60].

Contact co-crystallization

It has been found that the interaction between the API and the co-former can occur spontaneously after a "soft" mix of raw materials [61-63]. The proposed possible mechanisms that explain spontaneous crystallization by contact are vapor diffusion, moisture absorption, eutectic phase formation, amorphization, and long-range anisotropic molecular transfer of two solids [64]. High humidity, high temperature, and small particle size of the raw material may promote the formation of co-crystals [. Mac Fhionnghaile *et al.[*66] reported that caffeine and urea co-crystals were formed within 3 days by separately mixing pre-ground materials at room temperature and 30% relative humidity. The authors have shown that interparticle surface contact between solids is an important factor in the formation of caffeine-urea co-crystals. Ervasti *et al.*[67] demonstrated that the phase transition of the theophylline-nicotinamide physical mixture to co-crystals was achieved without the help of mechanical grinding. Another example of spontaneous crystallization is the co-crystallization of isoniazid and benzoic acid, in which the rearrangement of the co-crystals on the surface of isoniazid is in the presence of water by facilitating the interaction of isoniazid with benzoic acid vapor. This shows that it was accelerated at [68]. In addition, pre-grinding the co-crystal physical mixture reduced the induction time for co-crystal nucleation and increased the rate of co-crystal formation. Nartowski [69] also showed that adjusting the addition of water alters the kinetics of spontaneous co-crystal formation. The deliquescent of the malonic acid surface accelerated the conversion of caffeine-malonic acid co-crystals66. Ji *et al.*[70] showed that solvent vapors can act as catalysts to promote the formation of co-crystals of caffeine and malonic acid. Recently, it has been reported that co-crystals can be formed by exposing the co-crystal components to appropriate vapors [68,71,72]. Optical microscopic studies of moisture-induced carbamazepine-nicotine amide co-crystal formation have shown that component deliquescent controls co-crystal conversion and results in the local dissolution of solid materials for crystallization [73]. Huskie et al. [74] discovered a complex, multi-step dynamic pathway of co-crystal formation under methanol vapor using a benchtop powder X-ray diffractometer (Fig.). In the case of the carbamazepine-saccharin co-crystal, rapid formation of a short-lived crystalline phase was first observed, then disappeared within 30 minutes and changed to a monoclinic carbamazepine-saccharin type II co-crystal [74]. The conversion of carbamazepine-saccharin co-crystal type II to triclinic type I occurred after 1

hour. In addition, a 1: 1 nicotinamide superacid intermediate was first detected and then converted to a 2: 1 nicotinamide superacid co-crystal. This suggests that the formation was determined by competition with supramolecular synthons [74]. Similar observations were made in the nicotinamide fumaric acid co-crystal process, where the expected 2: 1 nicotinamide fumaric acid co-crystal was produced via a 1: 1 nicotinamide fumaric acid intermediate [74].

Solid State Grinding

The solid grinding method is widely used to produce co-crystal powder samples. Two forms are performed: (1) clean (dry) milling and (2) liquid assisted milling. Dry milling is a solvent-free co-crystallization process. The solid material that results in the co-crystals is mixed in appropriate stoichiometric quantities and compressed and ground together with a mortar and pestle or ball mill or vibration mill. The normal grinding time is 30 to 60 minutes. Many co-crystals can be created using this method, and failures are generally due to the use of improper settings. Decreasing particle size increases the specific surface area of interactions between materials for the development of intermolecular bonds. This offers the advantage of higher selectivity than co-crystallization by dissolution. It's simple and you can quickly create the co-crystals you need. It is also used as a way to clarify the priority of hydrogen bonds. However, dry milling problems include the absence of co-crystals, incomplete conversion to co-crystals, and crystal defects that can result in amorphous content. Similarly, incomplete conversion to co-crystal results in a mixture of co-crystals and excess starting material in the product, which is desirable as additional purification steps are required to obtain a pure co-crystal product. No [75].

Neat grinding

Previous studies have shown that the potential mechanisms of eutectic formation by simple grinding include molecular diffusion and the formation of transient and/or amorphous eutectic intermediates [76-77]. Abrasive molecular diffusion is the process of using an abrasive to create a moving solid surface that causes evaporation or energy transfer. Therefore, in a pure crushing process, high vapor pressure (10-110-4 mm Hg) of the solid components (at least one of the components) is required63. Therefore, vapor phase diffusion can lead to the formation of crystals on the crystal surface. In addition, grinding can provide energy for surface diffusion and migration, removing the generated crystals from the reactant surface and creating new surfaces for further crystallization [78]. For example, Rastogi *et*

al.[78] found that co-crystal formation of picric acid and aromatic hydrocarbons can be achieved by molecular diffusion using milling. In the eutectic induced co-crystallization process, (1) it is essential to continuously form a metastable eutectic liquid phase that is supercooled on a fresh solid surface and is produced by stirring. (2) Eutectic nucleation from the eutectic phase can then be induced by milling [76]. Chadwick *et al*. [76] observed a liquid eutectic phase at the solid surface under the microscope during the eutectic formation of diphenylamine and benzophenone. In addition, crystal nucleation leads to solidification in the liquid phase and can lead to crystal formation. For the amorphous crystal mediated mechanism, strong intramolecular interactions between APIs and covariates are the determinants of crystal formation [78]. Rodríguez Hornedo *et al*. [79] observed an amorphous phase when a mixture of carbamazepine and saccharin was spattered below the glass transition temperature, and co-crystal transformation occurred during storage at room temperature. Furthermore, the co-crystallization rate of carbamazepine and saccharin was increased by the addition of water. Rehder *et al*. [80] showed that the formation of piroxicam-citrate crystals is also a co-crystal process induced by an amorphous intermediate. A stepwise crystal formation mechanism has been proposed for pure grinding, where kinetic and thermodynamic crystal products are formed [78]. This is a common function when the reactant molecule contains a halogen or hydrogen binding site [81]. This mechanism is likely due to the hierarchy of strong and weak hydrogen bonding forces during crystal formation. Karki and associates. [81] and Halasz *et al.*[82] observed the step-by-step formation of a 2:1 nicotinamide super crystal by pure grinding. For Nicotinamide Superacid co-crystal 2:1 (NA2SUB). It is thought that NASUB formation is kinetically promoted by the strongest supramolecular building blocks of the carboxylic acid R2 (8) and the carboxylic acid pyridine R2 (7) (Figure). The thermodynamic product NA2SUB is stabilized by several slightly weaker building blocks of the amide building blocks R2 2 (8) and R2 2 (7) pyridine carboxylic acids.

Liquid-Assisted Grinding

This is a modification of the conventional grinding method. This involves mixing the two components and adding a very small amount of solvent (for example, a few tenths of a solvent per mole of component) during the milling process, which is a highly co-crystallizing reaction. Bring speed. In this process, the solvent functions as a medium that promotes molecular diffusion is an important factor in the formation of a multicomponent composite framework, and as a catalyst has been used to improve the supramolecular selectivity of the

crystal system. Do. The effect of the solvent can be explained as catalytic since its small amount is not part of the final product. Its advantages are improved efficiency, the ability to control polymorphism formation, and increased crystallinity of the product, making various isomers suitable for co-crystallization. With this method, after suitable grinding for a considerable time, some crystals have insufficient crystal-forming efficiency, resulting in an increase in the co-crystal ratio. Using this method, it is possible to produce crystals of high purity with greatly reduced production times. It also allows the synthesis of selective polymorphic crystal forms. This allows interconversion between crystalline polymorphic organic components, depending on the polarity of the solvent. The limitations of liquid-assisted milling machines include the fact that it is a small technology, require high energy consumption, and have poor performance in terms of product purity [83].

Hot Melt Extrusion Technique

Hot extrusion (HME) is a process that combines co-crystal formation and pharmaceutical formulation, providing an easier way to manufacture pharmaceuticals. In HME technology, the crystal plane unit is created by heating a powerful mixture of the drug and the molding agent. This improves surface contact without the use of solvents. The heat used in the HME process is set to a specific temperature at which only the matrix softens/melts. Crystal formation by the HME process requires a catalyst to enhance crystal formation induced by the softening/melting substrate. A suitable matrix for the HME process requires some quality. (1) It has a low glass transition temperature (Tg) and secures a processing temperature lower than the melting point of the co-crystal. (2) Noncovalent interactions with drugs or conformers are restricted. (3) Shows a rapid solidification step. The drawback of this methodology is that the coformer and API are incompatible with the liquefaction type and cannot be used for unstable drugs [84].

Miscellaneous co-crystal preparation

Laser Irradiation

This method uses a high-power CO_2 laser to irradiate previously co-crystal powder mixtures and induce their recrystallization into a co-crystal structure. Titapiwatanakun *et al.*used this method to produce crystals of caffeine with oxalic acid and malonic acid. These authors found that the co-crystal-forming substances must sublimate to a considerable extent for co-crystallization to occur, suggesting that the mechanism of molecular rearrangement between

the drug and conform molecules and Crystal nucleation is likely to occur in steam. stages [85].

Resonant Acoustic Mixing

Acoustic resonance mixing is used to mix the target molecule and the isomer in the presence of liquid to form crystals without any grinding media. In this method, mechanical energy is acoustically transferred into a wet powder mixture, initiating an intimate mixing of the ingredients. A series of carbamazepine crystals have been successfully produced using a resonant mixer operating at 80–100 G and 60 Hz. The co-crystal products have been isolated to a range of laboratory scales, 100 mg and 1.5 and 22 g, and the technology required to scale up [86]. Yearbook 2020, 62, 14 11 of 14

Freeze Drying

Freeze-drying or lyophilization is another approach that has been used to form pharmaceutical co-crystals. Recently, much effort has been made to adapt lyophilization to co-crystallization after it has become an established process with a number of applications in biotechnology, pharmaceuticals, diagnostics, and the food industry. Freeze-drying is a multi-step operation that involves drying by freezing a wet substance then subliming with ice directly into vapor by applying a low partial pressure of water vapor. This method is used as a processing technique to preserve a wide variety of products, including food and pharmaceutical products. Recently, this method has also been shown to be feasible for the preparation of new solid forms of the co-crystal system [87].

Electrospray Technology

Electro spraying is a process that simultaneously generates and charges droplets using an electric field. In this process, a solution containing solutes flows out from the capillary nozzle, held at a high voltage, through an electric field, causing the solution droplets to elongate to form a jet. The solution beam was dried and the generated particles were collected on a charged powder collector [87].

Microfluidic and Jet Dispensing Approaches

Microfluidics is a versatile technology that enables extremely high throughput analysis by running thousands of samples per second and controlling fluids in a network of micrometer channels. Under this platform, saturated solutions of parent and covariant compounds are

dissolved in different solvents in very small amounts for a single chipper combinator. Using a two-stage screening process, caffeine is treated with a variety of covariates and a variety of solvents to identify combinations with the highest propensity for crystals. The parent compound (caffeine) is inserted into the chip vertically, while the cofactor is introduced into the chip horizontally. The results demonstrated that co-crystal screening using microfluidic chips is reliable and reproducible [88].

Evaluation of co-crystals

1) Spectroscopic Analysis:

1.1. Fourier transforms infrared spectroscopy:

This is a widely used process to predict and determine the chemical structure, intermolecular interactions, and to study interactions between APIs and transforms. Analysis of the API, converter, and crystals was performed by FTIR in the wavelength range 400 to 4000 cm-1. This method is fast, non-destructive, susceptible to molecular changes, and can also detect a functional group.

1.2. Terahertz Spectroscopy Time Domain:

This technique is similar to X-ray powder diffraction (PXRD) for the characterization and identification of crystals. It is useful in distinguishing supramolecular, asymmetrical, and racemic structures present in a given sample. Examples include theophylline crystals with different compositions.

1.3. Solid State Nuclear Magnetic Resonance:

Solid-State NMR is commonly used to describe and identify various solid forms of pharmaceuticals, including co-crystals. This method determines salts and crystals as well as evaluates the structure by detecting local structural changes and hydrogen bonding by coupling the basic principle used in this method which is the displacement of nuclides by irradiation, different from Acts 2020, 62, 14 12 of 14 excipients. By this quantitative and qualitative technique, we can determine the molar ratio of the reaction mixture and the type of hydrogen atom present in a given molecule.

2.1 Thermal gravimetric method:

This method is useful for determining the mass of a sample under the influence of temperature over a specific period of time. Differential scanning calorimetry (DSC): Used to determine copper crystal formation, as determined by the existence of an exothermic peak followed by an endothermic peak in the DSC spectrum. The formation of crystals is determined by the presence of ridges (peaks) present in the compound. It is also useful in determining the melting point, polymorphic nature, glass temperature, heat of fusion, and exothermic or endothermic behavior of a compound or molecule. The thermogravimetric analysis provides accurate drying temperatures throughout the different reaction steps involved in the composition. This method is used to determine hydrated or solvated crystal forms, detect volatile components, and analyze decomposition or sublimation from crystals. Crystal purity, co-crystal solvate/hydrate forms, thermal stability, and compatibility with thermogravimetric methods can be predicted.

2.2 Hansen Solubility Study:

Hansen's solubility parameter is one of the important tools to predict the miscibility of a drug and its isomer during crystal formation or with excipients/carriers. It can also predict drug compatibility and its study is also useful for pre-and tablet formulation. Consolidation energy is used to predict physicochemical properties such as the melting point and solubility of a compound. The crystals are held together by weak hydrogen bonds and are miscible at the molecular level. In the solubility study, different types of solvents are used, such as water, different pH buffers, enteric stimulants, and gastric juices. It is one of the important parameters of screening tests for drug development.

2.3 Solubility Study:

It can be defined as "the amount of a drug substance that becomes a solution per unit time under specific conditions of liquid/solid surface, solvent composition and temperature". An in vitro solubility study of any solid drug is performed to evaluate the dissolution effect of the formulated drug. This study was performed on equipment that dissolves in the appropriate dissolution medium according to the official collections. Samples were taken at specified intervals and analyzed using an HPLC or UV spectrometer. Solubility Study The method of Higuchi and Connors was used to determine the solubility of crystals. The solubility of the

crystals, pure API, and physical mixture of API and coformer was determined in water and in another medium, as mentioned in the official documentation.

2.4 Stability study:

It is also one of the powerful parameters for crystallization [89] as it provides information on different storage climates and the shelf life of a drug or product. medicinal products. There are many parameters that affect drug stability, such as humidity, light, and temperature. Stability studies were performed under specific conditions of temperature and humidity over a predetermined period of time, providing detailed information on the shelf life of co-crystalline products under different storage conditions.

CONCLUSIONS AND FUTURE PROSPECTS

Crystals, especially pharmaceuticals, have become an important solid form in the pharmaceutical space. This is evident in the number of research articles, peer-reviewed articles published in 4,444 different journals as well as the organization of conferences and seminars over the past decade. From an industry perspective, the number of patents filed globally by various pharmaceutical industries and research groups is also growing at a rapid rate, as there are both regulatory and intellectual property implications. . Crystals are an excellent alternative for drug development to improve solubility, bioavailability, stability, and processability. However, there are still some challenges, including modulator selection, physicochemical characterization, and formulation. Careful examination of formulation design and adherence to can lead to successful crystal growth. In this review, we discuss in detail a wide range of application technologies for experimental screening, synthesis, and fabrication of pharmaceutical co-crystals in order to overcome the poor physical properties of APIs.

This review outline is provided on the proposed co-crystallization mechanisms to be formed by different techniques. At the beginning of development, co-crystallization processes mainly focused on traditional methods, such as solvent evaporation, grinding, and suspension methods. However, as time went on and the field evolved, scientists in the field developed new increasingly simple methods to enable co-crystallization processes to overcome previous limitations. here theirs. New methods that can be used for co-crystallization are hot-melt extrusion, spray drying, supercritical fluid technology, laser irradiation, freeze-drying, microfluidic and jet delivery, and more.

These methods successfully form a variety of pharmaceutical copper crystals. However, each method still needs to be thoroughly investigated to better understand the apparent. Co-crystallization mechanism for each method.

It is clear from the level of interest of both academia and the pharmaceutical industry that in the near future pharmaceutical co-crystals will be one of the viable and important solid pharmaceutical forms for i) re-engineering of existing drugs to improve performance. (ii) Lifecycle management with recently approved drugs. (iii) Allow the development of new compounds; performance and purification. (iv) Green chemistry and synthesis with co-crystalline intermediates.

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All authors have contributed equally.

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